RESPONSES TO COMMENTS SUBMITTED BY THE AMERICAN CHEMISTRY COUNCIL (ACC) ON VINYL CHLORIDE

Comment 1: A major shortcoming of the discussion of vinyl chloride in Appendix B is its failure to include much of the scientific literature from the past 20 years on the health effects of vinyl chloride exposure. This is inexplicable in light of OEHHA's acknowledgment of many of these studies in its Responses to Major Comments on Technical Support Document/Public Health Goal for Vinyl Chloride in Drinking Water (September 2000). Developmental and other studies highly relevant to the objective of protecting children's health, many of which OEHHA has discussed in previous documents, have been ignored. At the same time, OEHHA has chosen to include other studies (*e.g.*, Keilharn *et al*. (2000)), the relevance of which are unclear. The list of studies contained in the vinyl chloride section of Appendix B should be significantly revised to reflect the information contained in previous OEHHA documents and the recently completed Toxicological Review of Vinyl Chloride issued by the U.S. Environmental Protection Agency (EPA) on its Integrated Risk Information System (IRIS). Particularly puzzling is the absence of any apparent effort to achieve consistency with the EPA Toxicological Review. In response to recommendations of its Risk Assessment Advisory Committee, OEHHA indicated that it would collaborate with the federal EPA on risk assessment activities.

Response: Vinyl chloride was included among the eleven chemicals to be considered for differential effects on children primarily because of animal evidence that exposures at early ages may have a greater effect on cancer risk than exposures spread out over a lifetime. The review by Kielhorn *et al*. (2000) was included because it is a recent review of many aspects of vinyl chloride risk assessment, including exposure, epidemiological studies of cancer among exposed workers, and PBPK modeling. This paper deals with many of the same issues that are discussed in ACC's comments, so it certainly appears relevant to the discussion.

The draft OEHHA report reviewed only one study of reproductive and developmental effects (John *et al*., 1977). More developmental studies should be reviewed, particularly if they indicate possible developmental effects at relevant exposure levels. The draft document focused more on carcinogenicity, because it is in this area that OEHHA sees the most likely possibility of differential impacts on infants and children.

OEHHA's risk assessment for vinyl chloride differs from that of U.S. EPA because (as explained on page 11 of the draft document), CDHS chose a value at the top of a range of values calculated from human and animal studies, in acknowledgment of the fact that newborn animals showed greater sensitivity to the carcinogenic effects of vinyl chloride. U.S. EPA has chosen instead to use a 2X safety factor to account for the added risk to children. Some of the evidence suggests that this factor may not be adequate. The question of how best to quantify the added risk of early exposures to vinyl chloride has not yet been resolved. This is one of the best reasons to give vinyl chloride further consideration under the SB 25 program, which is intended in later stages to deal specifically with this dose-response issue.

It should be noted here that, as explained in the response to comment 3, OEHHA inadvertently used an old version of the table that is present in the OEHHA PHG document, which did not contain the newer epidemiology studies. We are correcting that mistake in the revision of the document.

In response to the commenter's issue that we are not being consistent with U.S.EPA, the OEHHA draft report is not a risk assessment document and the process of prioritizing the TACs for listing is not a risk assessment process. Rather, the process is a hazard identification process. Thus, the fact that EPA revised their quantitative assessment of the potency of vinyl chloride is not germaine to the issue at hand. In addition, we are in agreement with EPA in that both U.S.EPA and Cal/EPA believe there is established scientific evidence indicating that infants and children are more susceptible to the carcinogenic effects of vinyl chloride.

Comment 2: OEHHA uses a cancer slope factor of 0.27 $(mg/kg/day)^{-1}$ based on lung cancer incidence in female rats observed by Drew *et al.* (1983). Use of this potency factor is inappropriate for the reasons that follow.

The bioassay conducted by Drew *et al.* is not well suited for derivation of a cancer slope factor for vinyl chloride. First, Drew *et al.* provided for only one exposure level for each species. Based on this fact alone, EPA regards Drew *et al.* as inadequate to develop dose-response estimates, and therefore it is of little value to derive a cancer slope factor (IRIS Toxicological Review, Sec. 6.2.1). Second, OEHHA uses Drew *et al.* to support the conclusion that laboratory animals exposed to a carcinogen at a young age are at a higher risk for developing cancer later in life. However, the youngest animals exposed in Drew *et al.* were 8 to 9 weeks old, and thus approaching maturity, as noted by EPA (IRIS Summary, Sec. II.A.3). Other studies, such as those conducted by Maltoni *et al.* (1981, 1984) and used by EPA to develop a unit risk estimate for vinyl chloride, began exposure at 1 day of age. These other studies also used multiple exposure levels and showed dose-response. Third, OEHHA calculates a cancer potency factor with lung cancer data from Drew *et al.*, a less than ideal endpoint to use in light of the availability of cancer incidence data for more sensitive endpoints. As EPA recently noted, "the liver represents the most sensitive site for the cancer and non-cancer effects of vinyl chloride exposure" (IRIS Summary, Sec. II.A.2). OEHHA's rejection of Maltoni (1981, 1984) in favor of clearly limited data to calculate a cancer slope factor appears to be unjustified.

Furthermore, OEHHA's potency estimate relies on default factors that less accurately predict target tissue exposure than newer methodologies, such as the physiologically based pharmacokinetic (PBPK) modeling that EPA relied upon in its final Toxicological Review of Vinyl Chloride (Toxicological Review). In September 2000, OEHHA stated that "we would very much like to examine and include a new and verified PBPK modeling and methods such as might be found in a complete and final version of the EPA (1999a) document." (OEHHA Tech. Supp. Doc. for the Vinyl Chloride PHG, p. 32). At that time or shortly before, EPA made its final Toxicological Review available on IRIS. In regard to validation of the PBPK model on which EPA relied, the final Toxicological

Review contains a 48-page Appendix B that details the development and validation of the PBPK model. Some 50 articles from the scientific literature are referenced in this Appendix alone. Again, OEHHA's failure to use PBPK models in this case seems inconsistent with OEHHA's commitment to the Risk Assessment Advisory Committee to use new scientific methodologies in the TAC program.

It should be noted that the PBPK model used by EPA and the PBPK model published by Reitz *et al.* (1996) predict similar internal dose measures. Moreover, Reitz *et al.* reported that a unit risk of 5.7×10^{-7} $\mu g/m^3$ derived using data from Maltoni *et al.* (1981, 1984) overpredicted the number of tumors actually found in Simonato *et al.* (1991) (one of the major epidemiology studies) by 10- to 35-fold. Thus, not only has the PBPK model been validated, but its *over*conservatism has been documented in the scientific literature.

The net result of OEHHA's reliance on an unsuitable bioassay and rejection of PBPK modeling is that it overestimates cancer potency almost 20 times, *i.e.*, 0.27 $(mg/kg/day)^{-1}$ as compared with 0.015 $(mg/kg/day)^{-1}$, the equivalent of the current EPA unit risk estimate of 4.4×10^{-6} μ/m^3.[1] We urge OEHHA at a minimum, to accept the EPA risk assessment. If OEHHA continues to use a cancer potency factor almost 20 times higher than the one adopted by EPA, it should explain why it relies on an estimate so much higher than one that has been shown to overpredict the actual incidence of angiosarcomas observed in exposed worker populations by at least 100-fold.

Response: As explained in response to the first comment, CDHS chose to use the cancer potency based on the Drew study because it was at the top of a range of possible values calculated from human and animal data. This was done deliberately as a means of taking into consideration the potential added sensitivity of infants and children to vinyl chloride. Because there is evidence that exposures to infants and children may be more potent, a more health conservative estimate of cancer potency was deemed appropriate. Thus, OEHHA did not "reject" Maltoni or any other study; OEHHA (actually CDHS at the

[1] It overstates the risk 200 times compared to the PBPK estimate provided by Reitz *et al*., which in turn overpredicted the number of angiosarcomas actually observed in workers by at least 10-fold.

time) calculated cancer potencies based on several appropriate studies and chose a number at the top of the range for the reason explained above.

With regard to the question of why OEHHA has not performed a new risk assessment for vinyl chloride based in part on PBPK modeling, it is important to point out that the draft document we are discussing is not intended to be a risk assessment. It is intended to be a brief summary of available information with reference to the question of whether vinyl chloride would be likely to have greater toxic effects on infants and children than on adults. We used currently available values that have undergone the California process for risk assessment to help prioritize chemicals for listing TACs that may cause disproportionate impacts in infants and children. Considering all of the information available, it appears that vinyl chloride would be likely to have such an effect. The purpose of including it among the chemicals to be considered under the SB 25 program is to further evaluate this possibility. This further evaluation will be done in the future according to the timeline for considering these chemicals. The comments of the vinyl chloride panel are of interest but at this point in the process are not germaine to the discussion.

Comment 3: Appendix B erroneously states that "workers exposed to vinyl chloride appear to be at greater risk for brain cancer than are unexposed populations." The epidemiology studies upon which OEHHA relies in support of this conclusion are 20 or more years old. Most of these studies have been updated several times since 1981. The current scientific information supports the opposite conclusion.

A recent study sponsored by the Health Committee (Occupational Health Research Unit, Department of Medicine, University of Louisville, referred to hereafter as Lewis *et al.* (2000), showed no evidence of any relationship between exposure to vinyl chloride and brain cancer occurrence in the workforce at the manufacturing facility in Louisville, Kentucky which accounted for most of the excesses in brain cancer among American vinyl chloride workers noted in previous industry-wide cohort studies. In their study,

Lewis *et al.* specifically focused on whether brain cancer excesses at this facility were associated with occupational vinyl chloride exposure. The conclusions of Lewis *et al.* were consistent with the results of an earlier study of the same plant by the National Institute for Occupational Safety and Health (NIOSH). NIOSH concluded that "our data do not support the hypothesis that the excess risk of lung cancer and brain cancer which have been observed at this plant is associated with exposure to either VCM [vinyl chloride monomer] or PVC dust" (Wu *et al.* (1989)).

Mundt *et al.* (2000) conducted an industry-wide cohort study of American vinyl chloride workers including those at the Louisville plant. Mundt *et al.* updated and expanded upon the cohort of workers originally studied by Tabershaw and Gaffey (1974). [2] The number of workers included, the 25-year period over which they were monitored, and the breadth of occupational exposure information examined make Mundt *et al.* probably the single most important part of the scientific data base on vinyl chloride. Both Mundt *et al.* and Lewis *et al.* concluded that the earlier occurrence of brain cancer excess at the Louisville plant contributed to the findings of brain cancer excess in early industry-wide cohort studies. Mundt *et al.* noted that the brain cancer excess found among Louisville plant workers may be attributable to sustained exposure to some other carcinogen given their older age at first employment in vinyl chloride production. Table I in Appendix B should be revised and simplified in order to accurately reflect the current epidemiologic data base.

The conclusions of independent studies of European vinyl chloride workers also do not support the position that an increased risk of brain cancer results from vinyl chloride exposure. In a study sponsored by the International Agency for Research on Cancer (IARC), Simonato *et al.* (1991) concluded that, "[n]o significant excess of mortality was found for the other sites suspected *a priori* (*i.e.*, other than angiosarcomas of the liver) to be affected by exposure to VC." In a recent update of this study, *Ward et al.* (2000)

[2] Mundt *et al.* (2000) performed the most recent update, which supersedes earlier updates and reports by Tabershaw and Gaffey (1974), Cooper (1981), and Wong *et al.* (1991).

concluded that "[e]vidence for an association of brain cancer with VC exposure in the current study was generally negative."[3]

Three prominent scientists have independently reviewed the available American and European cohort data and concluded that they do not support an association between brain cancer (or any other malignancy except angiosarcoma of the liver (ASL)) and vinyl chloride exposure (Doll (1988); Blair and Kazerouni (1997); McLaughlin and Lipworth (1999)). Sir Richard Doll is the epidemiologist who helped identify the link between cigarette smoking and lung cancer. Aaron Blair is the director of the Occupational Epidemiology Division of the National Cancer Institute.

Doll stated that the small excesses in brain cancer are "not statistically significant" and that "there is nothing to suggest that they are occupational in origin." Blair and Kazerouni concluded that "[v]inyl chloride causes angiosarcoma of the liver, but a large, multi-country study provided no clear evidence that other sites are affected." McLaughlin and Lipworth found that "[h]ypothesized associations between vinyl chloride and cancers of other sites, namely lung, brain and lymphohaematopoietic system, are not consistently supported by the available data" and that "a comprehensive review of the relevant epidemiologic literature revealed that occupational vinyl chloride exposure has not been conclusively or causally linked to any adverse health outcome, with the exception of angiosarcoma of the liver." These conclusions are generally consistent with EPA's Toxicological Review of Vinyl Chloride (IRIS Summary, Sec. II.A.2).

In regard to other forms of cancer, the lack of adequate support for a causal link between occupational vinyl chloride exposure and non-ASL cancer applies even more emphatically in the case of lung cancer. Epidemiological evidence for this once suspected association no longer remains "inconclusive" (p. 6). Wu *et al.* (1989), Lewis *et al.* (2000), Mundt *et al.* (2000), and Ward *et al.* (2000) supercede older reports and show

[3] The IARC study examined cancer incidence among European workers employed in the vinyl chloride industry. Ward *et al.* (2000) performed the most recent IARC update. Ward *et al.* supersedes Byren *et al.* (1976), Fox and Collier (1977), Jones *et al.*, (1988), Pirastu *et al.* (1990), and Simonato *et al.* (1991).

either no excess or a deficit of lung cancer deaths. Since lung cancer mortality equates with lung cancer incidence in cohort studies, it cannot plausibly argue that these studies missed cases to any significant extent.

Appendix B states that "an association between vinyl chloride exposure and lymphoma has not been established" (p. 6). Once again, Appendix B appears to ignore the most important studies conducted in the last twenty years. As one example, Mundt *et al.* (2000) found a deficit in the number of cancers of the lymphatic and hematopoietic systems (71 observed deaths, SMR = 86, 95% CI 67 to 108). In his independent review of industry cohort data, Doll found no statistically significant excess in lymphoma among vinyl chloride workers. Weber *et al.* (1981), the principal study cited by OEHHA, did not find an excess in deaths due to lymphatic cancer. Furthermore, Weber *et al*. was conducted in Germany, where cause of death data historically have been unreliable. Thus, contrary to OEHHA's position, the available data refute any positive association between lymphatic cancers and occupational exposure to vinyl chloride.

OEHHA's failure to discuss the epidemiology studies from the past 20 years in Appendix B is perplexing in light of their appearance in the Technical Support Document for the Vinyl Chloride PHG published by OEHHA in September 2000. In revising the PHG Support Document to include these studies, OEHHA noted that it was "significantly strengthened as a result" (Responses to Major Comments on the PHG for Vinyl Chloride, p. 8).

Response: In preparing the draft summary OEHHA incorporated a table of epidemiological data from the PHG document (September, 2000). In doing so OEHHA inadvertently included an earlier version of the table that did not include some of the more recent epidemiological studies. OEHHA sincerely apologizes for this error. The draft document (including the table) will be revised to include the later studies cited in these comments. The later studies will be evaluated together with the older ones to arrive at a more balanced summary of all the results.

At this point it may be noted that the four later studies show SMRs for brain cancer that range from 1.07 (Simonanto *et al*., 1991) to 1.80 (Wong *et al*., 1991). None of these are statistically significant at the $p>0.05$ level. The fact that all four of them are greater than 1.00 (the expected level) suggests a positive association between vinyl chloride exposure and brain cancer. Ten of the eleven older studies also show SMRs greater than 1.00. The PHG document (which considered all of these studies) concluded, "Additionally, there is suggestive evidence for cancer of the brain, lung, and digestive tract in humans."

Regardless of our error in reporting on the occupational epidemiology studies on cancer, the draft report is not focusing on occupational studies as a premise for considering vinyl chloride as a TAC that may impact children disproportionately. Rather, our concern rests on the evidence for effects of age-at-exposure. Early life exposures increase both the amount of DNA-vinyl chloride metabolite adduct in the liver and the tumor yield in animal bioassays. This is powerful evidence that age-at-exposure influences cancer risk for this human carcinogen.

Comment 4: Appendix B fails to mention the results of the two-generation reproductive and developmental toxicity study in rats sponsored by the Health Committee in coordination with the Agency for Toxic Substances and Disease Registry (ATSDR) and reported to ATSDR and other interested federal and state agencies (including OEHHA) in 1998 (Thornton *et al*. (2001)).

Developmental toxicity is particularly relevant to protection of children's health. Inconsistent experimental design compromises the validity of the conclusions of the few studies that have examined the possible developmental and reproductive toxicity of vinyl chloride. Thus, failure to include any reference whatsoever to a recent guideline study of these endpoints is a major shortcoming in an assessment of potential impact on children's health.

The reproductive and developmental study sponsored by the Health Committee was designed to correct for several of the problems experienced in the past, including a lack

of maternal toxicity and inappropriate or deficient statistical analysis. The developmental study found no embryo-fetal or developmental toxicity for exposures ranging from 0 to 1100 ppm. The reproductive toxicity study found no adverse effect in the parental generations on mortality, clinical observations, body weight, or feed consumption, or effects on fertility or reproductive performance parameters.

A copy of the final report of the reproductive and developmental toxicity study was provided to OEHHA in March 2000, along with the conclusion that it "provided strong support for the conclusion that the liver and not the reproductive system is the critical target site for vinyl chloride." OEHHA noted that "[t]his was a valuable comment" and added a discussion of the study to the Technical Support Document for the PHG (Responses to Major Comments on the PHG for Vinyl Chloride, p. 6).

Response: Our draft document reviews only one developmental study, which is a negative study. This newer study is also apparently negative, so it would not change the general conclusions. However, the newer study should be included in the draft for the sake of completeness. Note that we have not used developmental toxicity as an endpoint in considering that vinyl chloride disproportionately impacts children. These negative developmental toxicity studies did not evaluate cancer as an endpoint and do not negate our concern that vinyl chloride may disproportionately impact infants and children..

Comment 5: An overwhelming amount of animal and epidemiological data confirm the liver as the organ most sensitive to vinyl chloride exposure (IRIS, pp. 11, 60, E-15). Furthermore, the evidence does not support a correlation with non-ASL cancers. Storm and Rozman (1997) performed an extensive, independent review of non-ASL cancer incidence due to vinyl chloride exposure and concluded that evidence for non-liver tumors is weak (IRIS Summary, Sec. II.A.2). Thus, protection against liver cancer will protect against other cancers as well (IRIS Summary, Sec. II.A.2).

In light of the evidence that confirms the liver as the most sensitive organ to vinyl chloride exposure and the strong support for a mechanism by which cancer is induced at this target organ, OEHHA should revise its risk assessment with deference to the exhaustive work of EPA. The decision by EPA to account for childhood sensitivity by applying a two-fold increase to a cancer potency factor derived in a conservative fashion from arguably the most appropriate animal bioassay was reviewed over a three-year period by independent experts before it was adopted.

Indeed, this is the approach supported by one of the few recent articles on vinyl chloride cited in Appendix B. Cogliano *et al.* (1996) argue that children are more susceptible to the carcinogenic effects of vinyl chloride than adults, and that "the potential for vinyl chloride to cause cancer is greatest for newborn exposure." They then propose an effective doubling of the risk estimate derived from Maltoni *et al.* (1981), the only study which in their view "provides direct information about this sensitive stage of development." If a differential impact on children is assumed, this would appear to be the more scientifically based way to address it.

Response: It was not the purpose of this draft document to do a risk assessment for vinyl chloride or to revise an earlier risk assessment. The purpose of the draft was to examine the question of whether vinyl chloride may potentially have a differential impact on infants and children either through differential toxicity, differential exposure, or both. The comments raise important questions about how a risk assessment for vinyl chloride should be performed in order to take into account differential susceptibility of infants and children. The approach that U.S. EPA has chosen (a 2X uncertainty factor) is one possible approach. OEHHA will have to consider this and other possible approaches in the future when it becomes necessary to reconsider the risk assessment for vinyl chloride as part of the SB 25 process.

As discussed above, CDHS calculated cancer potencies based on a number of endpoints including liver cancer and lung cancer. The endpoint that gave the highest cancer

potency was a lung cancer study (Drew *et al*., 1983). Thus it does not appear to be true that protecting against liver cancer would protect against all cancers.

The observation by Cogliano *et al*. that children are more susceptible to vinyl chloride than adults and that susceptibility would be highest for newborns are highly relevant to this discussion and are precisely the reason why vinyl chloride was included among the top eleven chemicals for consideration in this program.

Comment 6: Strict federal and state regulation has greatly reduced the possibility that the public, including children and other sensitive subpopulations, will ever be exposed to vinyl chloride. Virtually all known human exposure to vinyl chloride occurs at levels regulated by government agencies to be safe in occupational settings, where it is used primarily as feedstock material in polyvinyl chloride production. The Health Committee is aware of no evidence to suggest that current regulation has failed to protect public health and the environment.

Appendix B states that "[v]inyl chloride has not been detected in the ambient air of California at or above a detection limit of 0.5 ppb, except for measurements taken adjacent to vinyl chloride-related industries and landfills," and that only vinyl chloride emissions from "local hotspots" need to be assessed. This will be done, if appropriate, under the residual risk provisions of § 112 of the Clean Air Act and the California Air Toxics "Hot Spots" Information and Assessment Act. In light of the emphasis on public exposure as a criterion for selection and prioritization of TACs in the Children's Environmental Health Protection Act, and the existence of more targeted statutory authority to deal with any local concerns, OEHHA should remove vinyl chloride from the list of eleven candidate chemicals.

Response: As acknowledged in the draft document, exposure to vinyl chloride appears to be a local problem rather than a statewide ambient air problem. Based on exposure considerations, vinyl chloride would probably be less of a concern than other toxicants

that are present in the ambient atmosphere at levels of concern. This is why vinyl chloride was assigned to Tier 2 rather than Tier 1. Nevertheless, there are still local exposures to vinyl chloride near landfills and possibly other facilities. Additionally, the fact that vinyl chloride has been shown in animal experiments to have a higher cancer causing potential when the exposures occur early in life suggests that it should be considered for differential impacts on infants and children, which is the intent of SB 25.